Dealing with Uncertainty and Accounting for Social Value Judgments in Assessments of Orphan Drugs: Evidence from Four European Countries

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ABSTRACT

Objectives: To better understand the reasons for differences in reimbursement decisions for orphan drugs in four European countries that were not readily apparent from health technology assessment (HTA) reports and operating procedures. Methods: Semistructured interviews with representatives of HTA bodies in England, Scotland, Sweden, and France were conducted. An interview topic guide was developed on the basis of findings from a systematic comparison of HTA decisions for 10 orphan drugs. Qualitative thematic data analysis was applied to the interview transcripts using the framework approach. Results: Eight representatives from the four HTA bodies were interviewed between March and June 2015. Evidentiary requirements and approaches to dealing with imperfect or incomplete evidence were explored, including trial design and duration, study population and subgroups, comparators, and end points. Interviewees agreed that decisions regarding orphan drugs are made in a context of lower quality evidence, and the threshold of acceptable uncertainty varied by country. Some countries imposed higher evidentiary standards for greater clinical claims, which may be more challenging for orphan diseases. The acceptability of surrogate end points was not consistent across countries nor were the validation requirements. The most common social value judgments identified related to innovation, disease severity, and unmet need. Differences were seen in the way these concepts were defined and accounted for across countries. Conclusions: Although agreement was seen in evidentiary requirements or preferences, there were subtle differences in the circumstances in which uncertain evidence may be considered acceptable, possibly explaining differences in HTA recommendations across countries.

Keywords: health technology assessment, orphan drugs, rare diseases, value assessments.

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Introduction

Health technology assessment (HTA) aims to ensure that technologies offered are safe and efficacious and provide value for money [1]. Although value is often considered within the context of efficiency—reimbursements only the most efficient technologies within an allowable budget—this does not necessarily account for what matters most to patients or to society in general [2]. Indeed, certain aspects of value are difficult to capture and yet may provide benefits to both, such as innovation that results in a direct benefit to patients through improved prognosis or quality of life and also indirect societal benefits in terms of increased productivity and knowledge spillovers.

Despite using the same evidence and similar outcome measures and criteria, HTA assessments of a given drug may lead to contrary results in different countries [3]. This is particularly true with respect to orphan drugs, for which the general rules regarding appropriate evidence may be difficult to apply to small populations facing very serious chronic or life-limiting diseases [4]. Orphan drug trials are often characterized by lower quality evidence compared with nonorphan drugs [5,6]. Moreover, high acquisition costs often result in orphan drugs not being found to be cost-effective [7]. Nonetheless, orphan drugs often undergo the same HTA processes as drugs for more prevalent conditions.

In the face of imperfect evidence and high uncertainty in assessing orphan drugs, HTA bodies may rely on different attributes of value or approaches to dealing with imperfect evidence. Acceptability of uncertainty depends on the tools used to address uncertainty and on the judgment of the decision makers, who may consider additional qualitative criteria, such as disease or treatment characteristics [8].

Understanding the rationales underlying conflicting decisions is challenging. Although the internal regulations of HTA bodies explain the operating framework and the opinions or recommendations document the evidence considered and the basis for the decision, certain subtleties may not be captured even in the most complete documentation. A better understanding is therefore needed about how HTA bodies value orphan drugs and deal with issues of rarity.

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We previously analyzed the decisions of 4 HTA bodies for 10 orphan drug-indication pairs on the basis of the opinions and in light of each entity’s internal regulations [9], and we explored scientific and social value judgments used in the assessment of orphan drugs [10]. A number of reasons for differences in HTA recommendations were identified throughout the decision process and across countries. Building on these findings, this study aimed to develop a broader perspective about how value is assessed for orphan drugs and how differences affect reimbursement decisions on the basis of interviews of representatives of four European HTA bodies.

### Methods

Purposeful sampling was used to select the study countries, each of which undertakes assessments using well-established processes and criteria, has publicly available reports, and represents a cross selection in terms of HTA approach and perspective (Table 1). These included the National Institute for Health and Care Excellence (NICE, England), the Scottish Medicines Consortium (SMC, Scotland), the Dental and Pharmaceutical Benefits Board (Tandvårds- och läkemedelsförmånsverket, Sweden), and the French National Authority for Health (Haute Autorité de Santé [HAS], France). HTA body representatives from each study country were identified by partners of a European research consortium, Advance-HTA [11]. These HTA bodies have either regulatory or advisory roles, in which their decisions will be automatically implemented in the former and accounted for by the final decision maker in the latter (Table 1). Furthermore, orphan drugs do not have a special status in the study countries, with the exception of SMC, in which greater uncertainty or higher incremental cost-effectiveness ratios (ICERs) may be accepted if the requirements for their modifiers are fulfilled [12].

We conducted semistructured interviews using an interview topic guide developed by the lead author and reviewed by all co-authors (see eAppendix A in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.03.005). It included open-ended questions derived from actual scenarios that arose in the context of our cross-national comparison of 10 orphan drugs. Interview questions were divided into themes, including 1) the general evidentiary requirements for orphan drugs regarding primary and nonprimary evidence, trial duration, and clinical and surrogate end points; 2) other evidence and considerations around quality-of-life data and qualitative criteria (innovation, safety, and uncertainty, 2) comparators, 3) treatment outcomes and incremental cost-effectiveness ratios (ICERs) may be accepted if the requirements for their modifiers are fulfilled [12].

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Qualitative thematic data analysis was undertaken using the framework approach [13]. Subthemes within each general theme were identified and inductively coded, and a matrix was created to facilitate comparison of each subtheme across the four HTA bodies. The key findings from each of these subthemes were summarized in tables that incorporated illustrative quotes. The initial findings were discussed among the co-authors, and a list of follow-up questions was developed to complement the interviews in which information was unclear or incomplete. These additional questions were sent to each interviewee along with the summary findings for their particular HTA body for confirmation. Results focused on the contrasts across countries identified within each theme. Themes were reorganized as follows: 1) clinical evidence and uncertain, 2) comparators, 3) treatment outcomes and safety, and 4) additional qualitative criteria.

Each theme portrays the agencies’ perspectives about the clinical evidence appraised and whether evidence for orphan drugs is characterized by greater uncertainty compared with drugs for more prevalent conditions. The evidence base used for HTA is imperfect or incomplete, and therefore uncertain, because it relies on estimated values from experimental or observational studies [14–16]. Decision makers make scientific value judgments about the extent to which uncertain evidence is acceptable. These judgments include whether the evidence presented fully and accurately captures the effect of the intervention, whether it is generalizable to the local context of the decision, whether quality-of-life changes are accurately captured, or whether it is appropriate to impose restrictions to population subgroups [14]. We aimed to obtain additional insights on the appraisal processes in terms of the HTA bodies’ approaches to dealing with uncertain evidence, including the circumstances under which imperfect or incomplete evidence that does not accurately capture the effect of the intervention may be deemed acceptable.

### Results

Eight representatives from the four HTA bodies were interviewed between March and June 2015. Interviewees occupied senior positions in their agencies (e.g., Head of the Technology Appraisal Programme, Head Economist or Pharmacist, and Chair of the Appraisal Committee). Interviews were conducted face-to-face and, in one case, by telephone, lasting 1 to 3.5 hours. Responses

### Table 1 – Study countries, HTA bodies, and types of HTA.

<table>
<thead>
<tr>
<th>Study country</th>
<th>HTA body</th>
<th>Type of HTA</th>
</tr>
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<tbody>
<tr>
<td>England</td>
<td>NICE: National Institute for Health and Care Excellence (regulatory body)</td>
<td>Clinical and cost-effectiveness, national health and personal social services perspective</td>
</tr>
<tr>
<td>Scotland</td>
<td>SMC: Scottish Medicines Consortium (advisory body to the NHS boards)</td>
<td>Clinical and cost-effectiveness, national health and personal social services perspective</td>
</tr>
<tr>
<td>Sweden</td>
<td>TLV: Dental and Pharmaceutical Benefits Board (regulatory body)</td>
<td>Clinical and cost-effectiveness, societal perspective</td>
</tr>
<tr>
<td>France</td>
<td>HAS: Haute Autorité de Santé (Comité de la Transparence) (advisory body to the Ministry of Health)</td>
<td>Benefit-risk ratio, clinical benefit driving the coverage rate (SMR), and relative improvement in clinical benefit driving the pricing scheme (ASMR)</td>
</tr>
</tbody>
</table>

ASMR, relative improvement in clinical benefit (“Amélioration du Service Médical Rendu”); HTA, health technology assessment; NHS, National Health Service; SMR, clinical benefit (“Service Médical Rendu”).
Clinical Evidence

Trial design
None of the HTA bodies imposes formal requirements regarding minimum levels of evidence for orphan drugs, although phase III comparative trials are preferred. HAS also requires all existing and available data at the time of the HTA submission.

A notable distinction was seen in expectations about the quality of evidence submitted when examined within the context of the clinical claim. The TLV has higher scientific and methodological demands for superior efficacy with a price premium, and greater uncertainty is accepted for noninferior efficacy (and low price) or for treating otherwise untreatable diseases. HAS judges the quality of the evidence according to the situation of the disease in terms of prevalence and recruitable patients, and the highest relative improvement in clinical benefit ("Amélioration du Service Médical Rendu") (ASMR) rating should demonstrate a positive effect on survival.

Trial duration
In considering the appropriate trial duration, all the HTA bodies are concerned about the likely durability of response. NICE and HAS also account for the natural progression of the disease. The TLV looks to the European Medicine Agency’s assessment for guidance in this regard, whereas NICE and SMC look to the
Summary of product characteristics supplied by the marketing authorization holder (MAH). Overall, the SMC, TLV, and HAS were more willing than NICE to accept greater uncertainty on treatment duration for orphan drugs.

Registry data
Although rarely used, the agencies agreed that registry data and historical controls are acceptable when no other data are available (NICE), when these are the best data available (SMC, TLV), to collect long-term data on safety and efficacy or on disease progression when no alternative treatments exist (HAS), for economic modeling purposes (NICE), or when the disease is rare or other special circumstances are seen (SMC). The limited use of historical controls may be explained by the lack of knowledge about the type of data useful in the future (NICE), missing data such that comparisons become inappropriate (HAS), or poor data quality.

Fig. 2 – Visual representation of interview responses (treatment outcomes and safety). EQ-5D, EuroQol five-dimensional questionnaire; HAS, Haute Autorité de Santé; HTA, health technology assessment; NICE, National Institute for Health and Care Excellence; SMC, Scottish Medicines Consortium; TLV, Dental and Pharmaceutical Benefits Board.
Study population and subgroup data
In general, prespecified subgroup data are preferred by all bodies. Post hoc subgroup data may be accepted if the subgroup corresponds to the licensed or trial indication (HAS) or depending on its relative size and potential significance (SMC). Nevertheless, extrapolating treatment effects from subgroup data to a wider population would not be accepted by HAS. For the other agencies, preference would be given to the subgroup driving the results.

Comparators
Subtle differences were seen in the selection criteria for comparators. NICE uses a scoping process before appraisal to identify the appropriate comparator. The other countries consider the comparators put forward by the MAH. Judgment about their appropriateness is generally based on clinical expertise and local clinical guidance.

Treatment Outcomes and Safety
The choice of relevant clinical end point varies across countries. The SMC judges the appropriateness of the end points provided in the MAH’s submission. For HAS, the choice depends on the situation of the disease (e.g., short-term consequences) and the aim of the drug (e.g., symptoms for a symptomatic treatment). NICE and TLV prefer survival data, which would then feed into the quality-adjusted life-year estimate.

The acceptability of surrogate end points depends on their validation against an end point (hard or soft), although HAS insists on a hard end point in such cases. A nonvalidated end point would probably not be accounted for by NICE, whereas it may be accepted under certain circumstances by the others. Surrogate end points for orphan drugs are more likely to be accepted by HAS if no other option is available and by the SMC if it fulfills one of its defined modifiers. NICE and TLV are not more likely to accept surrogate end points for orphan drugs.

There were different levels of acceptability for the surrogate end point progression-free survival. NICE always prefers overall survival to progression-free survival even if it is the trial’s secondary end point. Progression-free survival is accepted by the SMC when there is an established link with life extension or the main benefit is improved health-related quality of life (HRQOL). The TLV also prefers overall survival but acknowledges that it is often not available and thus relies on progression-free survival, which is considered to be potentially closer to patients’ needs. For HAS, progression-free survival would not replace overall survival in a situation in which life expectancy is very short unless it were a validated surrogate of overall survival.

HRQOL data were considered either as a hard end point (NICE, TLV, and SMC) or as a soft end point (HAS). The TLV recognized the challenges in collecting HRQOL data for rarer conditions, but the SMC did not consider these challenges to be specific to orphan drugs.

Safety is not part of the assessment for NICE, SMC, and TLV because it is already assessed as part of the drug’s marketing authorization. Nonetheless, safety may be considered by the SMC and NICE to the extent it affects quality-adjusted life-year gains or is not adequately captured by utility, survival, and cost estimates. HAS, however, assesses safety along with efficacy. The agencies also agreed that safety may modulate the assessment of efficacy (e.g., if efficacy is the same and safety is worse).

Additional Qualitative Criteria Considered
The interviews provided additional insights into the relevant evidence and weight of each of the criteria innovation, unmet need, and disease severity (Table 2). NICE explicitly accounts for innovation, defined as a step change for patients rather than as a new class of drug or mechanism of action, whereas the TLV and SMC do not have specific criteria. HAS gives innovative drugs higher ASMR ratings (I, II, III), which result in European pricing rather than a lower negotiated price. Likewise, innovative hospital drugs are covered over and above applicable diagnosis related group (DRG) tariffs.

For NICE, unmet need is accounted for in drugs with high ICERs by looking at how a patient’s HRQOL is affected without treatment rather than improved survival, which is considered to be captured by the model with its baseline severity. The TLV also explicitly accounts for severity in accepting higher ICERs. Disease severity corresponds to a greater unmet medical need, although no explicit weighing or definition of severity currently exists. The SMC does not explicitly account for severity, although committee members may intrinsically capture this element. For HAS, severity is incorporated into its Service Médical Rendu (SMR) ratings that drive coverage levels. Predefined categories of severity have been defined: severe, life-threatening, short life expectancy, affects quality of life, not so severe.

NICE and TLV consider disease severity and unmet need together by focusing on the consequences of refusal to cover the drug. NICE also accounts for the drug’s place in the therapeutic strategy given the medical need and would recognize an unmet need when no other treatment options are available. The SMC assesses unmet need on a case-by-case basis, drawing on clinical expertise to understand current treatment options and how the new treatment would fit into clinical practice. Unmet need would be recognized through the application of a decision modifier (“lack of available treatments proven efficacy”), which is strictly applied when there is no proven treatment available for a particular indication. Thus, a situation in which there is no treatment at all would likely have priority over one for which few treatments exist. The existence of intolerable side effects would also give rise to a recognition of unmet need. HAS considers unmet need in the context of assessing the place of the treatment in the therapeutic strategy, which includes identification of comparators. If no other options were available, this would be considered a great unmet need.

Discussion
This study aimed to elicit the views of HTA bodies about their approaches to valuing orphan drugs. HTA bodies agreed that the evidence for orphan drugs is of lower quality than that for drugs for more prevalent conditions. Despite the broad agreement seen in evidentiary requirements or preferences, subtle differences were identified with respect to the circumstances under which this imperfect or incomplete evidence may be considered acceptable, which might influence HTA outcomes and explain differences across countries.

Despite the known limitations in generating robust evidence for orphan drugs [4,9], formal evidentiary requirements are similar for orphan and nonorphan drugs, with the exception of HAS, which accounts for the situation of the disease, when a small trial population and noncomparative trial would be considered acceptable if the number of patients living with the disease was very low. The TLV and HAS have higher evidentiary requirements for superior efficacy, which has implications for orphan drugs when the lack of treatment options increases the likelihood that a new treatment would be superior [6]. Demonstrating survival or other clinically relevant patient benefits requires well-designed large trials [17,18]. For orphan drugs, greater treatment effects would be required from small-scale trials to attain statistical significance [19], unless innovative small-scale trials are designed [20].
<table>
<thead>
<tr>
<th>HTA body</th>
<th>Innovation</th>
<th>Unmet need</th>
<th>Severity</th>
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<tr>
<td>NICE</td>
<td>Defined by whether the treatment benefits patients, determined during the deliberative process For example, delaying chemotherapy, first oral treatment replacing intravenous administration; counterexamples: new class of drugs, new mechanism of action (without visible benefits to patients)</td>
<td>Defined by the consequence of the decision, determined during the deliberative process in which NICE is willing to accept a higher ICER (up to £30,000/QALY) for the conditions with a high unmet need For example, effect on quality of life of patients without treatment</td>
<td>Defined by the consequence of the decision, determined as part of the deliberative process in which NICE is willing to accept a higher ICER (up to £30,000/QALY) for the more severe diseases. For example, effect on quality of life of patients without treatment</td>
</tr>
<tr>
<td>SMC</td>
<td>Intrinsic to the decision, likely captured differently; anything providing benefits to patient, captured by the ICER or accounted for during the deliberative process For example, a first in class could fulfill an unmet need, new mode of action or administration benefits, advantages in terms of service delivery, reduced severe adverse events, step change in patient management</td>
<td>For orphan drugs through the modifiers, “lack of available treatments of proven efficacy,” determined as part of the deliberative process and from clinical experts “No treatment” would be prioritized over “few treatments.” If there were “few treatments” with intolerable side effects, it would be considered an unmet need</td>
<td>No definition, may be accounted for intrinsically during the deliberative process</td>
</tr>
<tr>
<td>TLV</td>
<td>Benefits to patients, captured by the ICER or as part of the deliberative process For example, improved administration form benefits patients and reduces costs</td>
<td>Defined by the consequence of the decision, determined as part of the deliberative process Disease severity and unmet need are considered to be related: the greater the severity, the greater the unmet need</td>
<td></td>
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<tr>
<td>HAS</td>
<td>Captured within the ASMR; a drug with an ASMR I, II, or III would be considered as innovative. Prices would be set at European levels and would not be negotiated with the economic committee (CEPS)</td>
<td>Captured within the SMR; place in the therapeutic strategy: if no other options at the same stage of the disease, on the basis of the analysis of comparators and the description of therapeutic strategy (how the disease is treated, where the drug would fit, and what are the current existing alternatives) For example, a real unmet medical need would be recognized when there are no other treatment options</td>
<td>Captured within the SMR; different categories of severity defined: severe, life-threatening, short life expectancy, affects quality of life, not so severe</td>
</tr>
</tbody>
</table>

Table 2 – Information about innovation, unmet need, and severity.

ASMR, relative improvement in clinical benefit (“Amélioration du Service Médical Rendu”); CEPS, economic committee (“Comité Economique des Produits de Santé”); HAS, Haute Autorité de Santé; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life-year; SMC, Scottish Medicines Consortium; SMR, clinical benefit (“Service Médical Rendu”); TLV, Dental and Pharmaceutical Benefits Board.

Countries applied similar criteria in assessing appropriate trial duration, which were related to the natural course of the disease and likely duration of the treatment. Challenges, however, exist in defining the appropriate trial duration for orphan drugs, particularly when the natural history of the disease is unknown [4] or when the disease is chronic or has an early onset. Orphan drugs are often characterized by short clinical testing phases [6], which may not be sufficiently long to capture their benefits in clinical practice, particularly for lifelong conditions.

Registries are particularly useful for rare diseases by collecting information about the patient experience and natural history of the disease, thereby improving the quality and reliability of this evidence [21]. The use of registries, however, remains limited because of their time-consuming nature and challenges in analyzing historical evidence of a product’s effectiveness [22]. This was confirmed by the interviewees.

Regarding subgroups, the HTA bodies generally preferred prespecified subgroups and imposed restrictions when cost-effectiveness was driven by a subgroup of patients. The situation was different for HAS, which requires subgroups to be similar to those considered for marketing authorization or included in the trial. Orphan drugs often treat rare diseases of genetic origin that affect children. Of the 81 orphan drugs receiving marketing authorization since 2000, half are authorized for a subgroup of children and another 34 are under investigation in children [23]. In addition, 30% to 40% of orphan drugs treat different cancers, which are characterized by an increasing body of research on predictive biomarkers to assess
treatment response [24]. Despite this, very few subgroups of different subtypes are included in licensing indications and those that do may fail to reflect clinical practice [23]. A review of 894 randomized controlled trials showed that half reported subgroup analyses, of which 46% were planned in the trial protocols and only 10% matched those reported in the publication [26]. Thus, subgroup data must be assessed with caution. Given the frequency of subgroup data in rare diseases because of their heterogeneity, lack of knowledge about existing subtypes [4], and licensing of orphan drugs for adult patients in diseases that commonly affect children [27], new methods are needed to address these issues beyond simply restricting the indication, such as imposing re-assessments, providing coverage contingent upon evidence development, and collecting real-world data through registries.

Issues regarding comparative evidence are more frequent for orphan drugs given that they often rely on single-arm, non-randomized studies [6] and that expertise about clinical pathways may be lacking [4]. This also implies that there are likely to be greater differences across countries in their definitions of standard care pathways. Therefore, it may be even more challenging to produce comparative trials with the appropriate comparators for a particular clinical context.

Surrogate end points are more common for orphan drugs than for nonorphan drugs [6,28]. Differences in acceptability of end points for validation (hard vs. soft) may have implications for orphan drugs, given questions about their clinical relevance (e.g., improvement in walking or platelet response) [25] or difficulties in establishing their validation [19]. Evidence suggests that surrogate end points tend to overestimate treatment effects, which may be minimized by quantifying their magnitude and validating them with relevant patient outcomes [30]. This issue also underscores the need to ensure that what is being measured improves clinical practice [35]. Nonetheless, the study is not without limitations. First, the interview questions were derived from the analysis of 10 orphan drugs. Although this sample may not be representative of all issues surrounding orphan drugs, the scenarios encountered were repeated, suggesting that the most common types of issues encountered were captured. The main advantage of focusing the interview questions on scenarios is that it allowed comparison with what was seen in practice. Second, varying levels of detail may have been captured during the interviews. To address this, a second round of questions with tables summarizing responses to the initial interview was sent to all interviewees to ensure comparability and reliability of the research. Third, the differentiation between how these findings apply to orphan and nonorphan drugs, which undergo the same assessment process, was at times unclear. We, nevertheless, were able to identify certain issues specific to orphan drugs and to explore how the process could be adapted to overcome some of these unique challenges.

Conclusions

Orphan drugs, which generally are subject to the same processes as drugs for more prevalent conditions, are assessed in a context of lower quality evidence, and this study contributed to understanding how HTA bodies address these challenges. Although agreement was seen regarding evidentiary requirements and preferences, differences were apparent in how this imperfect or incomplete evidence was considered, which may explain conflicting recommendations. This study further identified systemic features that are not well adapted to assessment of orphan drugs, which may need to be reconsidered to ensure that their value is appropriately captured when used to inform reimbursement decisions. This is all the more compelling in a pharmaceutical environment that is shifting toward more niche and targeted therapies in which HTA bodies will increasingly face such issues.

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Supplemental Materials

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REFERENCES